Original Article

Efficacy of omega-3 fatty acids for hospitalized COVID-19 patients: a systematic review and meta-analysis of randomized controlled trials

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Background and Objectives: Emerging expert consensuses and guidelines recommend that omega-3 fatty acids may have anti-inflammatory effects in hospitalized patients with coronavirus disease (COVID-19). However, these recommendations are based on pathophysiological studies of inflammation rather than direct clinical evidence. We conducted this systematic review and meta-analysis to evaluate the efficacy of omega-3 fatty acid supplementation in hospitalized patients with COVID-19. **Methods and Study Design:** We retrieved literature from PubMed, Web of Science, Embase, China National Knowledge Infrastructure (CNKI), WANFANG, Chinese Biomedical Literature Database, and Cochrane Library databases up to May 1, 2023. Data from studies comparing omega-3 fatty acids with a placebo or other pharmaceutical nutrients were analyzed. **Results:** Of 3032 records, 42 full-text articles were reviewed, five eligible studies were identified, and one study was found in the references. In total of six studies involving 273 patients were included, pooled, and analyzed. Compared to the control group, omega-3 fatty acid intervention reduced the overall mortality of hospitalized patients with COVID-19 (RR=0.76; 95% CI, [0.61, 0.93]; p=0.010). No serious or unexpected drug-related adverse events were observed. No statistical significance was observed in inflammatory markers such as CRP (MD=-9.69; 95% CI, [-22.52, 3.15]; p=0.14; I^2=97%) and IL-6; however, the neutrophil/lymphocyte ratio was significantly lower in the omega-3 FAs group on day 7 of intervention ($p < 0.001$). **Conclusions:** Omega-3 fatty acid administration may be associated with reduced mortality in hospitalized patients with COVID-19. Given the small sample size of enrolled studies, more rigorous and large-scale trials are urgently needed in the future to verify its efficacy.

Key Words: SARS-CoV-2, COVID-19, omega-3 fatty acids, pandemic, mortality

INTRODUCTION

Coronavirus disease (COVID-19) is one of the most disruptive public health crises in the world. Although the peak of pandemic waves has passed, the disease will coexist with human society for the next many years.[1] Despite unprecedented efforts, the number of infections and deaths remain high.[2, 3]

Omega-3 fatty acids are polyunsaturated. Eicosapentaenoic acid (EPA) and docosahexaenoic acids (DHA) are the major active components of omega-3 fatty acids.[4] Given its performance in improving immune function, omega-3 fatty acids have been considered a potential regimen for critically ill patients with COVID-19.[3] Recently, emerging expert consensus and guidelines have recommended that omega-3 fatty acid regimens may be effective in treating hospitalized patients with COVID-19.[5, 6, 7, 8, 9, 10, 11] However, the rationale behind these recommendations was mainly based on empirical deductions as growing evidence shows that omega-3 fatty acids play

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crucial roles in immune regulation in T-cell immunity, especially the proliferation of CD4+ T cells, and the drop in the CD4 cell level of patients with severe COVID-19/critical patients with COVID-19 is related to the increased risk of death;[12, 13, 14, 15, 16, 17] the use of omega-3 fatty acids may improve oxygenation and down-regulate the inflammatory storm.[12, 18, 19]

Most expert consensus and guidelines on the implementation of omega-3 fatty acid regimens are based on experiences related to inflammatory illness in general and a lack of specific clinical evidence in patients with COVID-19.[5, 6, 7, 8, 9, 10, 11] Therefore, we conducted a systematic review and meta-analysis to evaluate the efficacy of omega-3 fatty acid supplementation in hospitalized patients with COVID-19.

METHODS

Protocol and registration

We designed and implemented a meta-analysis and systematic review as per the PRISMA Statement. Details of the protocol programs were recorded in PROSPERO with registration ID-CRD42023411706.

Inclusion criteria

The inclusion criteria were implemented in accordance with the PICOS principle)

P (participants): hospitalized patients with COVID-19

I (intervention): omega-3 fatty acids

C (comparison): placebo or other pharmaceutical nutrients

O (outcomes): primary outcome: overall mortality, adverse events

secondary outcomes: inflammatory markers, renal function, liver function, lymphocytes

S (study design): randomized controlled trials (RCTs)

Exclusion criteria

Exclusion criteria were as follows: (1) pregnant and lactating women; (2) patients who are allergic or intolerant to omega-3 fatty acids; (3) patients with cancer; (4) patients with a history of immune system disorders; and, (5) patients whose expected time of survival ≤24 hours

Literature sources and retrieval strategy

We obtained access to literature databases and retrieved all the articles available in databases of PubMed, Web of Science, Embase, China National Knowledge Infrastructure (CNKI), WANFANG, Chinese Biomedical Literature Database, and Cochrane Library databases up to May 1, 2023. The retrieval process is summarized in Supplementary Table 1.

Literature screening and data extraction

The selection and data collection processes were conducted rigorously according to the PRISMA guidelines. Two reviewers (YHY and WY) meticulously implemented this program. Controversies were addressed through guidelines and consultation. Data extracted included demographic indicators of the patients included in the study, measures of intervention and control, statistics of overall mortality, adverse events, inflammatory markers such as CRP and IL-6, neutrophil/lymphocyte ratio (NLR), renal and liver function, CD4 T cell counts, and lymphocyte counts.

Quality assessment

The Revised Cochrane risk-of-bias tool (RoB 2) was used to assess the risk of bias in the RCTs. This tool covers five domains of bias that can affect the results of RCTs: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and bias in the selection of reported results. Two researchers (YHY and YW) independently assessed the quality of the included trials. Any disagreement was resolved by a third researcher (JH).

Statistical analyses

Dichotomous and continuous variables were analyzed and pooled separately using different methods. The values of the risk ratio (RR) and 95% confidence interval (CI) of the dichotomous variables were determined using the Mantel–Haenszel method. For continuous variables, the values of mean difference (MD) and 95% CI were calculated using the inverse variance method. The statistical test level α was set at 0.05. Statistical differences were considered significant at $p < 0.05$. Statistical heterogeneity existed when $I^2 \neq 0$, and high heterogeneity existed when $I^2>50\%$. Random-effects models were used when heterogeneous results were obtained ($I^2 > 0$).[20] Otherwise, a fixed-effects model was used. Furthermore, a subgroup analysis was performed considering the type and age of the patients. Publication bias was evaluated when the number of eligible studies exceeded 10 because an inadequate number of studies weakened the power of the tests. A sensitivity analysis was performed to verify the robustness of the results. Review Manager 5.4 was used for the data analysis.

Evaluation of certainty and importance for evidence

Using the online tool GRADEpro,[21] we evaluated the certainty and importance of the evidence step-by-step. Assessment items of certainty for evidence included but were not limited to the initial study design, risk of bias, imprecision, indirectness, and inconsistency. By this guideline, the certainty for evidence was rated as “high,” “moderate,” “low,” or “very low” using GRADEpro. Meanwhile, the same tool was used to rate the importance for evidence from to 1–9 and was eventually classified into three levels: “not important, important, critical”.

RESULTS

Literature retrieval results and study, and demographic characteristics

According to the retrieval strategy above, 3032 records were acquired initially, and one eligible record was discovered from the references. Duplicate articles were excluded by browsing the titles and abstracts. Further, 43 studies were retained after a rigorous selection process, and 37 were excluded. Only six studies met all inclusion criteria.[15, 22, 23, 24, 25, 26] Overall, 273 patients were included in this systematic review and meta-analysis. The interventions were administrated for five or seven days. The follow-up period was 30 d. The characteristics of the includ-

ed studies and demographic indicators are presented in Supplementary Tables 2 and 3, respectively. The literature retrieval and selection processes are shown in Figure 1.

Quality assessment

The plots for each risk of bias program and overall percentages across the six RCTs are shown in Supplementary Figures 1 and 2, respectively.

Primary outcomes

Overall mortality

Overall mortality was reported in four RCTs.[15, 22, 23, 24] Of the 200 hospitalized patients with COVID-19, 106 deceased. Pooled data indicated that omega-3 fatty acid intervention reduced the overall mortality in patients with COVID-19 (RR=0.76; 95% CI, [0.61, 0.93]; p=0.010), without heterogeneity between studies (I^2=0%). The detail is shown in Figure 2. The certainty of evidence was deemed low, and its importance was rated as critical.

Adverse events

Five RCTs involving 172 hospitalized patients with COVID-19 reported adverse events, side effects, or complications.[22, 23, 24, 25, 26] No serious and unexpected drugs-related adverse events, side effects, or complications were encountered during the follow-up period, indicating that the treatment with omega-3 fatty acids in patients with COVID-19 was safe and reliable. The certainty of evidence was deemed low, and its importance was rated as critical.

Secondary outcomes

Inflammatory markers

CRP (mg/L)

Five studies reported CRP levels during hospitalization in 172 patients with COVID-19.[22, 23, 24, 25, 26] Three of the five studies could not be pooled because the CRP outcome was not reported as the mean and standard deviation (SD).[22, 23, 24] The remaining two studies involving 73 hospitalized patients with COVID-19 were pooled.[25, 26] The pooled data showed that omega-3 fatty acid supplementation may not be associated with lower CRP after treatment because the statistical difference between the two groups was not significant (MD=-9.69; 95% CI, [-22.52, 3.15]; p=0.14; I^2=97%). The detail is shown in Supplementary Figure 3. The certainty of evidence was deemed very low, and its importance was rated as important.

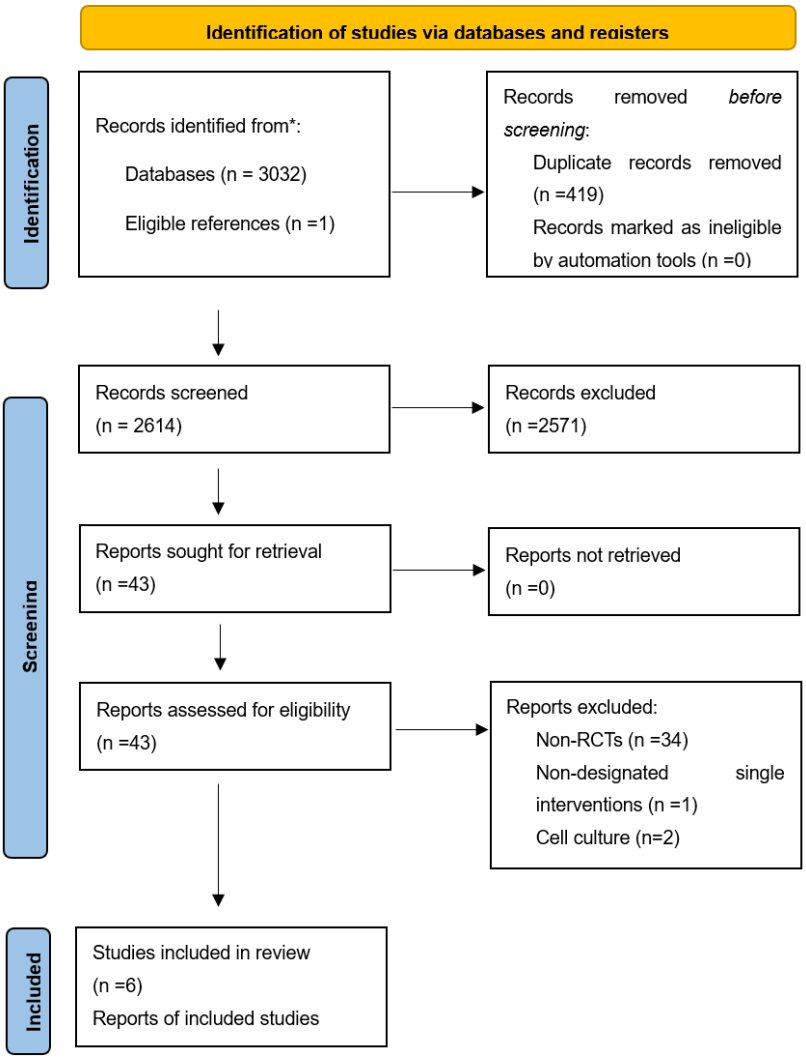


Figure 1. Research results. Name of database and number of studies searched: PubMed (n=294); Embase (n=1741); Web of Science (n=794); Cochrane Library (n=54); SinoMed (n=4); CNKI (n=17); WANFANG Data (n=128)

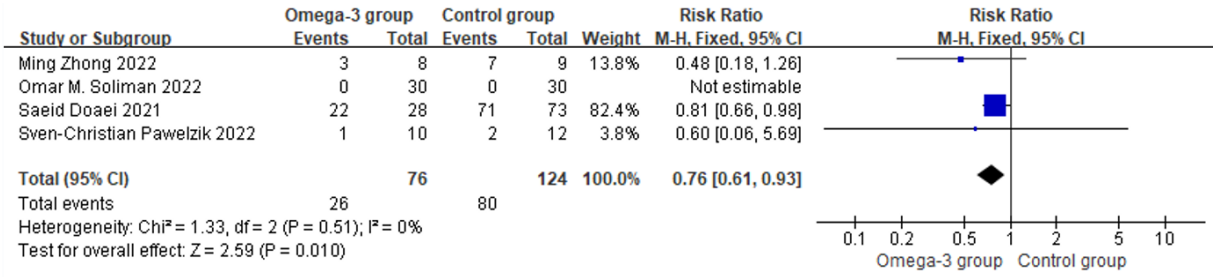


Figure 2. Forest plot of comparison: overall mortality

IL-6 (pg/mL)

Two studies reported IL-6 during hospitalization in 82 patients with COVID-19.[22, 24] The results of these two studies could not be pooled; one study reported the results as a supplementary figures without specific values,[22] whereas, in the other study with 60 patients, from admission to the 7th day, values of IL-6 changed from 6.91 pg/ml and 7.13 pg/ml to 7.40 pg/ml and 7.80 pg/ml in the two groups, respectively.[24] No statistically significant differences were observed between the groups. The certainty of evidence was deemed very low, and its importance was rated as important.

Neutrophil/lymphocyte ratio (NLR)

One study with 60 patients reported the NLR.[24] There was no statistically significant difference in the NLRs of the two groups until the 7th day. The NLR for the experimental and control groups rose from 5.60 and 5.25 on admission to 6.10 and 9.65 on day 7 respectively. The ratio was significantly lower in the experimental group on day 7 ($p<0.001$). The certainty of evidence was deemed very low, and its importance was rated as important.

Renal function

Cr (mg/mL)

Two studies involving 161 patients reported Cr.[15, 24] The results of the two studies could not be pooled as the outcome Cr in one study was not reported as a mean±SD,[24] whereas the other study with 101 patients showed the Cr to be significantly lower in the omega-3 fatty acid-treated group (1.29±0.24 vs 1.68±0.15 mg/mL, p=0.02).[15] The certainty of evidence was deemed low, and its importance was rated as important.

BUN (mg/mL)

Only one RCT involving 101 patients with COVID-19 reported BUN.[15] The result showed that the BUN was much lower in the omega-3 fatty acids-treated group (35.2±4.10 vs 43.2±2.50 mg/mL, p=0.03). The certainty of evidence was deemed very low, and its importance was rated as important.

Urea (mg/dL)

Only one RCT involving 60 patients with COVID-19 reported urea,[24] which reported no statistically significant difference between two groups on the 7th day after treatment [17.0 (11.0–22.0) vs 20.0 (11.0–29.0) mg/dL, p=0.366]. The certainty of evidence was deemed very low, and its importance was rated as important.

Urine volume (mL)

Only one study involving 101 patients with COVID-19 reported a difference in urine volume between the two groups;[15] omega-3 fatty acid intervention significantly increased the urine volume significantly by 224 mL (2101±884 vs 1877±917, p=0.01). The certainty of evidence was deemed very low, and its importance was rated as important.

Liver function

ALT (U/L)

Two studies involving 90 patients with COVID-19 reported ALT after treatment.[24, 25] The results could not be pooled, as one study did not report the ALT in the form of mean±SD; therefore, the results of the two studies were reported separately. One study involving 60 patients showed that there was no statistically significant difference between the two groups on the 7th day after treatment [21.0 (15.0–31.0) vs 29.0 (15.0–37.0) U/L, p=0.321].[24] The other study involving 30 patients also showed no statistically significant difference between the two groups after treatment (22.6 ± 1.63 vs 24.3 ± 1.69 U/L, p=0.71).[25] The certainty of evidence was deemed very low, and its importance was rated as not important.

AST (U/L)

Two studies involving 90 patients with COVID-19 reported AST after treatment.[24, 25] However, the results could not be pooled, as one study did not report AST in the form of mean±SD; therefore, the results of the two studies were reported separately. One study involving 60 patients showed that there was no statistically significant difference between the two groups on the 7th day after treatment [23.0 (18.0–35.0) vs 30.0 (18.0–37.0) U/L, p=0.549].[24] The other study involving 30 patients also showed that there was no statistically significant difference between the two groups after treatment (33.1 ± 2.68 vs 37.0 ± 2.57 U/L, p=0.26).[25] The certainty of evidence was deemed very low, and its importance was rated as not important.

Lymphocyte count

Two studies involving 144 patients with COVID-19 reported the lymphocyte levels after treatment.[15, 26] However, the results could not be pooled because of different measurement units; therefore, the results of the two studies were reported separately. One study involving 43 patients showed that there was no statistically significant difference between the two groups on the 8th day after treatment (2064±158 vs 2272±210 cells/mm^3, p=0.258),[26]

whereas the other study with 101 patients showed that the count of lymphocytes was significantly reduced in the omega-3 group after interventions (11.6±0.81 vs 11.8±0.73 $*10^6$/L, p=0.05).[15] The certainty of evidence was deemed very low, and its importance was rated as important. No study reported CD4 T cell counts.

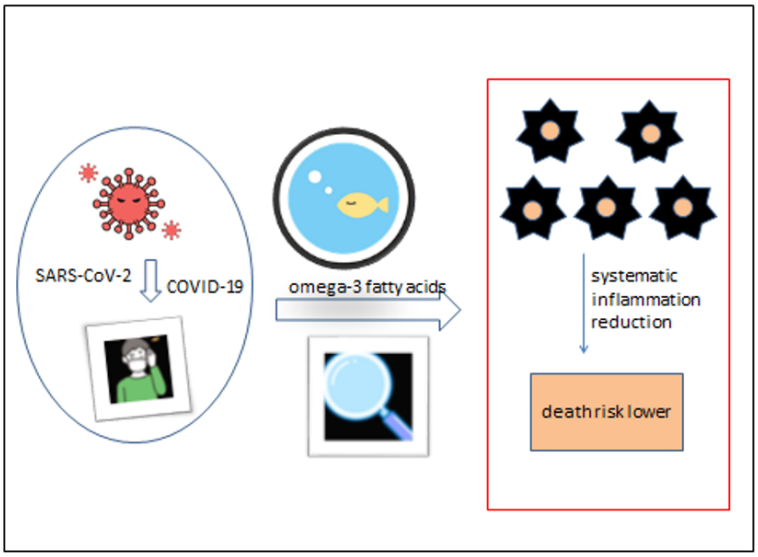
GRADE summary of evidence table for key outcomes based in RCTs

We used the GRADEpro to evaluate the certainty of the evidence. The details are presented in Supplementary Table 4. Considering that the number of eligible RCTs and patients was limited and the clinical characteristics of the patients in the six RCTs were different, which was linked to potential heterogeneity, the results should be viewed with caution. As a result, the overall certainty of the evidence and the importance of this systematic review and meta-analysis are regarded as very low and important.

DISCUSSION

We systematically reviewed the efficacy of omega-3 fatty acid intervention in the treatment of hospitalized patients with COVID-19. To the best of our knowledge, this work is the first of its kind. Given the rigor and comprehensiveness of systematic reviews and meta-analyses, we reviewed related studies regarding omega-3 fatty acids in hospitalized COVID-19 patients. The pooled results of our meta-analysis indicated that treatment with omega-3 fatty acids was associated with mortality reduction significantly (RR=0.76; 95% CI, [0.61, 0.93]; p=0.010), without heterogeneity (I^2=0%). This conclusion was in agreement with those of other non-RCTs; however, we reported more persuasive evidence on the safety and reliability of omega-3 fatty acid supplementation. According to Stromberg et al., patients with moderate and severe COVID-19 manifested lower levels of plasma fatty acids than those with mild COVID-19 and healthy adults, but their study lacked direct evidence to elucidate the safety and reliability of fatty acid supplementation, let alone omega-3 fatty acids.[27] Asher et al. reported a strong trend between omega-3 fatty acid supplementation and reduced mortality in hospitalized patients with COVID-19.[18] In addition, a national survey that included over 110,000 participants reported that the habitual dietary intake of fish oil, although not linked with SARS-CoV-2 infection, was linked with lower hospitalization and mortality in patients infected with SARS-CoV-2.[28] Zapata B et al. further confirmed the inverse outcomes between a lower omega-3 index and death due to severe COVID-19, with and without adjustment for well-known risk factors such as age and sex.[29] The findings from these non-RCTs are indirect evidence for a relationship between low omega-3 and mortality, therefore, we laid the foundation for the broader applications of omega-3 fatty acids in patients with COVID-19 to reduce death rate.

However, our study also found some controversies. Cytokine storm is recognized as the most important mechanism leading to severe disease and even death in patients with COVID-19.[1, 19] Excessive cytokine levels and hyperactivation of the immune system attributed to cytokine storms lay heavy burdens on bodies and cause sustained damage to vital organ systems. Given the already proven powerful anti-inflammatory effects in other inflammatory diseases, treatment with omega-3 fatty acids in patients with COVID-19 appears to be promising and appealing.[17] An *in-vitro* cell culture experiment by Chiang et al. corroborated that omega-3 fatty acids, such as DHA and EPA, could function as anti-inflammatory and anti-infection drugs to fight SARS-CoV-2 in human endothelial progenitor cells.[30] Pimentel et al.'s RCT provided patients with oral nutrients containing omega-3 fatty acids and observed a dramatic reduction in serum CRP, concomitant with a dramatic increase in lymphocyte counts.[26] Further, Sedighiyan et al. evaluated the efficacy of omega-3 fatty acids and concluded that a continuous two-week supplement with 2 g of moderate-dose omega-3 fatty acids was sufficient to modulate CRP, erythrocyte sedimentation rate, and other systemic inflammatory indicators.[25] We found that the NLR was significantly lower after omega-3 fatty acids intervention on day 7. However, in our pooled analysis, no statistical significance was ob-



Graphical abstract. of omega-3 fatty acids for COVID-19

served in inflammatory markers such as CRP (MD=-9.69; 95% CI, [-22.52, 3.15]; p=0.14; I^2=97%) and IL-6; In addition, no significant improvement was observed in lymphocyte count after treatment. We believe these inconsistent results may due to the small sample size and the differences on the sampling time-points.

We compared the differences in liver and kidney functions between the two groups. Patients in the omega-3 group showed significant improvements in creatinine, BUN, and urine volume. The ALT and AST did not significantly differ between the two groups. The pooled results indicated that omega-3 fatty acids administration is safe.

Limitations of our study

Our study had some limitations. We included a limited number of eligible patients because of the limited number of trials on omega-3 fatty acid supplementation. For the same reason, we were unable to provide evidence on the optimal timing and dosage of omega-3 fatty acids in patients with COVID-19 at different disease stages. The effect of omega-3 fatty acids on inflammatory marker levels and lymphocyte count in patients with COVID-19 is still controversial. Therefore, more rigorous trials are urgently required. No study reported CD4 T cell counts.

Conclusions

Studies have shown that omega-3 fatty acids significantly reduce mortality in patients with COVID-19 without adverse events. The effects on inflammatory marker levels varied between studies. No significant improvements were observed in liver function or lymphocyte count. The use of omega-3 fatty acids is safe. Considering the small sample sizes of the enrolled studies, more rigorous and large-scale trials are urgently needed in the future to verify its efficacy.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare that they have no competing financial interests or personal relationships that may have influenced the work reported in this study.

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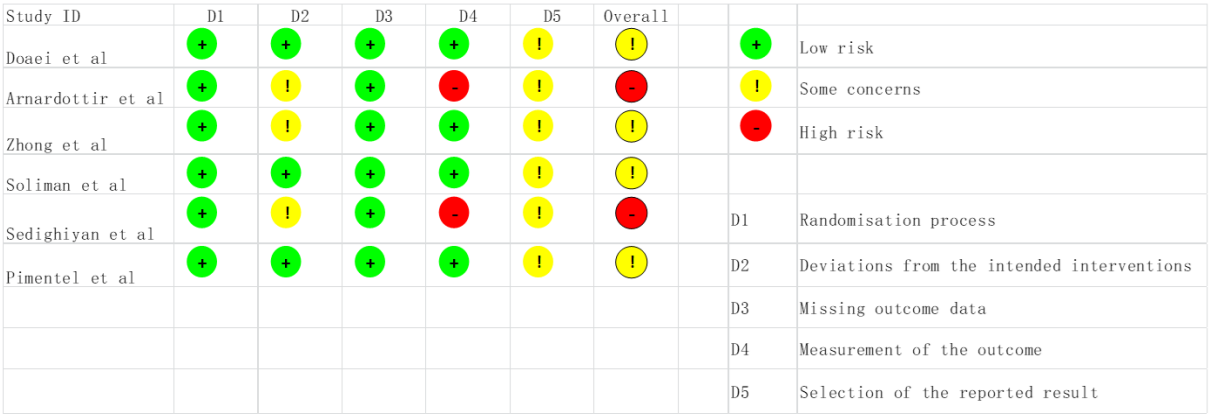
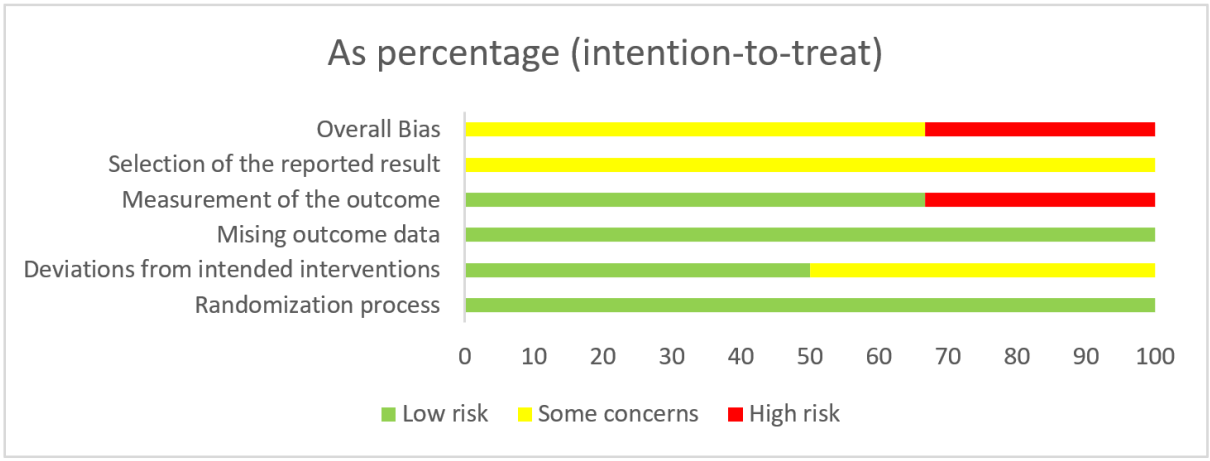
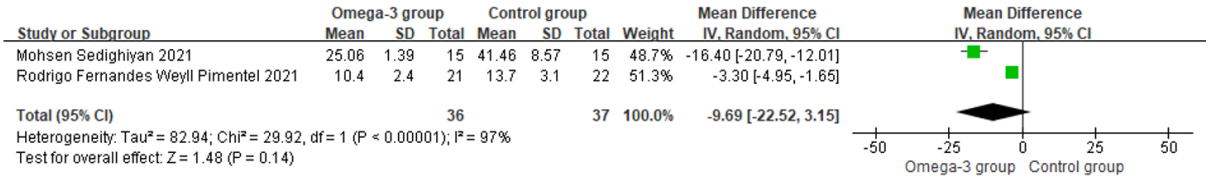
Supplementary Figures and Tables



Supplementary Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Supplementary Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Supplementary Figure 3. Forest plot of comparison: CRP

Supplementary Table 1. Search strategy

Database	Strategy
PubMed	(((COVID-19[Title/Abstract]))OR(SARS-CoV-2[Title/Abstract]))AND (((((((Omega-3[Title/Abstract]))OR(Ω-3[Title/Abstract]))OR(ALA[Title/Abstract])) OR(EPA[Title/Abstract]))OR(DHA[Title/Abstract]))OR(fish oil[Title/Abstract]))
Embase	#11 #9 AND #10 #10 #3 OR #4 OR #5 OR #6 OR #7 OR #8 #9 #1 OR #2 #8 'ω 3' #7 'omega 3'/exp OR 'omega 3' #6 ('fish'/exp OR fish) AND ('oil'/exp OR oil) #5 'dha'/exp OR dha #4 epa #3 ala #2 'sars cov 2'/exp OR 'sars cov 2' #1 'covid 19'/exp OR 'covid 19'
Web of Science	1: TS=(COVID-19) 2: TS=(SARS-CoV-2) 3: TS=(Ω-3) 4: TS=(Omega-3) 5: TS=(ALA) 6: TS=(EPA) 7: TS=(DHA) 8: TS=(fish oil) 9: #1 OR #2 10: #3 OR #4 OR #5 OR #6 OR #7 OR #8 11: #9 AND #10
Cochrane Library	#1 (Omega-3):ti,ab,kw #2 (Ω-3):ti,ab,kw #3 (ALA):ti,ab,kw #4 (EPA):ti,ab,kw #5 (DHA):ti,ab,kw #6 (fish oil):ti,ab,kw #7 (COVID-19):ti,ab,kw #8 (SARS-CoV-2):ti,ab,kw #9 #1 or #2 or #3 or #4 or #5 or #6 #10 #7 or #8 #11 #9 and #10
SinoMed	("xinguan"[changyongziduan:zhineng])AND ("Omega-3"[changyongziduan:zhineng] OR " Ω -3"[changyongziduan:zhineng] OR "ALA"[changyongziduan:zhineng] OR "EPA"[changyongziduan:zhineng] OR "DHA"[changyongziduan:zhineng] OR "yuy-ou"[changyongziduan:zhineng])
CNKI	(Subject:Omega-3(jingque))OR(Subject:Ω-3(jingque))OR (Subject: ALA(jingque))OR(Subject:EPA(jingque))OR (Subject:DHA(jingque))OR(Subject: yuyou(jingque))AND ((Subject: xinguan(jingxuan)))
WANFANG	(((((Subject="Omega-3") OR Subject=" Ω -3") OR Subject="ALA") OR Subject="EPA") OR Subject=DHA OR Subject=yuyou) AND (Subject="xinguan")

Supplementary Table 2. Characteristics of studies included

	Arnardottir et al	Zhong et al	Soliman et al
Registration in Trial Registries	European Union Drug Regulating Authorities Clinical Trials database with number 2020-002293-28 and at Clinical Trials.gov with number NCT04647604	Chinese Clinical Trial Registry (ChiCTR2000029851)	ClinicalTrials.gov PRS(NCT04957940)
Country or region	Sweden	China	Egypt
Study Design	RCT	RCT	RCT
Blinding	Single-blind	Single-blind	Double-blind
Funding source	Government	Government	None
Setting	Karolinska University Hospital	JinYinTan Hospital	Assiut University
Recruitment period	June 2020 to December 2020	February 2020 to March 2020	NR
Sample size	22	17	60
Intervention	once daily i.v. infusion (2 mL/kg) of Ω-3 PUFA emulsion (Omegaven ®) containing 10 g of fish oil per 100 mL, of which 1.25-2.82 g DHA and 1.44-3.09 g EPA	ALA (1200mg/d, intravenous infusion) once daily on top of standard medical care	Intravenous fish-oil-based lipid (SMOF lipid 20%) emulsion supplementation in a dose of 100 ml/day at a rate of 12.5 ml/h over 8 h
Control	once daily i.v. infusion (2 mL/kg) of placebo (0.9% NaCl)	equal volume saline infusion on top of standard medical care	standard enteral nutrition plus 100 ml/day of 0.9% normal saline at a rate of 12.5 ml/h over 8 h
Duration of the intervention	5 days	7 days	5 days

	Sedighiyan et al	Pimentel et al
Registration in Trial Registries	Iranian Registry of Clinical Trials (IRCT) with ID number: IRCT20200511047399N1	Brazilian Registry of Clinical Trials (REBEC) under UTN No.U1111-1252-3270
Country or region	Iran	Brazil
Study Design	RCT	RCT
Blinding	Single-blind	Double-blind
Funding source	NR	Authors funded the study themselves
Setting	Amir- Alam Hospital	a hospital specialized in caring patients diagnosed with COVID-19 in the city of Salvador
Recruitment period	February 2020 to April	from July to December 2020
Sample size	30	43
Intervention	receive omega- 3 (3 capsules containing 670 mg EPA and DHA + 2 capsules containing 400 mg Hydroxychloroquine)	received two 200 mL units of a normocaloric, high-protein nutritional supplement with some L-arginine, nucleotides, and ω-3 essential fatty acids (Impact ®, Nestlé) distributed over 24 hours. Every 100 mL of this supplement provided 109 kcal, 6.5 g of protein, 14 g of carbohydrate, and 2.8 g of fat, without fiber and lactose
Control	receive 2 capsules containing 400 mg hydroxychloroquine	received two 200 mL units of a normocaloric, high-protein nutritional supplement without the addition of any immunonutrition component (Nutren Senior ®, Nestlé) distributed over 24 hours. Every 100 mL of this supplement provided 98 kcal, 8.0 g of protein, 9.4 g of carbohydrate, and 3.2 g of fat, without fiber and lactose
Duration of the intervention	14 days	7 days

NR: not reported

Table 3. Demographic characteristics between two groups among included studies[†]

Study	Arnardottir et al		Zhong et al		Soliman et al	
	Omega-3 (n = 10)	Control (n = 12)	Omega-3 (n = 8)	Control (n = 9)	Omega-3 (n = 30)	Control (n = 30)
Demographic characteristics						
Age, yr	80.7 ± 7.0	81.5 ± 5.6	62.5 (59-67)*	63 (58-65)*	61.1 ± 6.56	61.5 ± 6.79
Sex, male ,n (%)	5 (50%)	5 (42%)	6 (75%)	7 (77.78%)	21 (70.0%)	19 (63.3%)
BMI, kg/m²	26.3 ± 4.4	25.0 ± 5.6	-	-	32.2 ± 2.96	32.4 ± 2.48
Smoker, n (%)	2 (20%)	0 (0%)	-	-	16 (53.3%)	17 (56.7%)
Oxygen-support, n (%)[‡]	-	-	8 (100%)	9 (100%)	6 (20.0%)	14 (46.7%)
SOFA	-	-	3.75 ± 2.05	4.33 ± 2.00	-	-
Coexisting conditions, n (%)						
Cardiovascular disease[§]	5 (50%)	9 (75%)	1 (12.50%)	0 (0%)	-	-
Hypertension	6 (60%)	9 (75%)	4 (50%)	4 (44.4%)	3 (10.0%)	4 (13.3%)
Diabetes	6 (60%)	3 (25%)	1 (12.50%)	3 (33.3%)	2 (6.7%)	2 (6.7%)
COPD/Asthma	2 (20%)	1 (8.3%)	-	-	-	-
CKD	3 (30%)	2 (17%)	-	-	-	-
Rheumatological disease	2 (20%)	2 (17%)	-	-	-	-

Study	Doaei et al		Sedighiyan et al		Pimentel et al	
	Omega-3 (n = 28)	Control (n = 73)	Omega-3 (n = 15)	Control (n = 15)	Omega-3 (n = 21)	Control (n = 22)
Demographic characteristics						
Age, yr	66 ± 14.6	64 ± 14.3	66.5 ± 2.89	67.1 ± 2.28	41.1 ± 2.8	41.9 ± 2.6
Sex, male ,n (%)	15 (53.60%)	45 (61.6%)	9 (60%)	9 (60%)	14 (66.7%)	12 (54.6%)
BMI, kg/m²	27.7 ± 7.54	27.4 ± 3.15	27.0 ± 0.94	26.1 ± 0.73	27.3 ± 1.2	27.8 ± 1.0
Smoker, n (%)	2 (7.1%)	5 (7.1%)	0	0	-	-
Oxygen-support, n (%)[‡]	-	-	-	-	-	-
SOFA	-	-	-	-	-	-
Coexisting conditions, n (%)						
Cardiovascular disease[§]	-	-	-	-	-	-
Hypertension	-	-	-	-	-	-
Diabetes	-	-	15 (100%)	15 (100%)	-	-
COPD/Asthma	-	-	-	-	-	-
CKD	-	-	0	0	-	-
Rheumatological disease	-	-	0	0	-	-

n: numbers; SOFA: sequential organ failure assessment; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease

[†]Demographic data is expressed as either mean ± standard deviation or numbers and percentage. (*represents median and interquartile range). Dashes indicate data not reported

[‡]Oxygen-support: Ambient air, Nasal or mask oxygen, High-flow oxygen or non-invasive ventilation, invasive ventilation.

[§]Cardiovascular disease was defined as medical history of at least one of the following: coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, atrial fibrillation, venous thromboembolism

Supplementary Table 4. GRADE summary of evidence table based on RCTs

Certainty assessment							Number of patients	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omega-3 fatty acids	Placebo or other pharmaceutical nutrients
Overall mortality								
4	Randomised trials	Serious[†]	Not serious	Not serious	Serious[‡]	None	26/76 (34.2%)	80/124 (64.5%)
Adverse events								
5	Randomised trials	Serious[†]	Not serious	Not serious	Serious[‡]	None	0/84 (0.0%)	0/88 (0.0%)
CRP								
2	Randomised trials	Serious[†]	Very serious[§]	Serious[¶]	Serious[††]	None	36	37
IL-6 level								
2	Randomised trials	Serious[†]	Serious[‡‡]	Serious[§§]	Very serious[††]	None	40	42
NLR								
1	Randomised trials	Serious[†]	Not serious	Not serious	Very serious[††]	None	30	30
Cr level								
2	Randomised trials	Serious[†]	Not serious	Not serious	Serious[††]	None	58	103
BUN								
1	Randomised trials	Serious[†]	Not serious	Not serious	Very serious[††]	None	28	73
K								
2	Randomised trials	Serious[†]	Not serious	Not serious	Serious[††]	None	58	103
Urea								
1	Randomised trials	Serious[†]	Not serious	Not serious	Very serious[††]	None	30	30
Urine volume								
1	Randomised trials	Serious[†]	Not serious	Not serious	Very serious[††]	None	28	73
ALT								
2	Randomised trials	Serious[†]	Not serious	Serious[¶¶]	Very serious[††]	None	45	45
AST								
2	Randomised trials	Serious[†]	Not serious	Serious[¶¶]	Very serious[††]	None	45	45
Lymphocyte count								
2	Randomised trials	Serious[†]	Very serious[†††]	Serious[‡‡‡]	Serious[††]	None	49	95

CI: confidence interval; MD: mean difference; RR: risk ratio

[†]without allocation concealment; [‡]included patients <300

[§]I^2=97%

[¶]intervention group (receiving Hydroxychloroquine plus 2 g of Docosahexaenoic acid [DHA] + Eicosapentaenoic acid [EPA]) and an immunonutrient-enriched supplement respectively

[††]included patients <400

[‡‡]one study reported the results as a supplementary figures without specific values

[§§]Control: standard enteral nutrition and placebo (0.9% NaCl) in two groups respectively

[¶¶]one intervention group (receiving Hydroxychloroquine plus 2 g of Docosahexaenoic acid [DHA] + Eicosapentaenoic acid [EPA]) and fish-oil-based lipid emulsion (FOBLE) supplementation in another intervention group

[†††]One study involving 43 patients showed that there was no statistically significant difference between the two groups on the 8th day after treatment, whereas the other study with 101 patients showed that the count of lymphocytes was significantly reduced in the omega-3 group after interventions

[‡‡‡]the intervention: fortified formula with n3-PUFA or a supplement enriched with immunonutrients in two studies respectively

Supplementary Table 4. GRADE summary of evidence table based on RCTs (cont.)

	Effect		Certainty	Importance
Number of studies	Relative (95% CI)	Absolute (95% CI)		
Overall mortality				
4	RR 0.76 (0.61 to 0.93)	155 fewer per 1,000 (from 252 fewer to 45 fewer)	⊕⊕◯◯ Low	CRITICAL
Adverse events				
5	Not estimable		⊕⊕◯◯ Low	CRITICAL
CRP				
2	-	MD 9.69 lower (22.52 lower to 3.15 higher)	⊕◯◯◯ Very low	IMPORTANT
IL-6 level				
2	-	See comment	⊕◯◯◯ Very low	IMPORTANT
NLR				
1	-	Not estimable	⊕◯◯◯ Very low	IMPORTANT
Cr level				
2	-	See comment	⊕⊕◯◯ Low	IMPORTANT
BUN				
1	-	Not estimable	⊕◯◯◯ Very low	IMPORTANT
K				
2	-	MD 0.14 lower (0.18 lower to 0.1 lower)	⊕⊕◯◯ Low	IMPORTANT
Urea				
1	-	Not estimable	⊕◯◯◯ Very low	IMPORTANT
Urine volume				
1	-	Not estimable	⊕◯◯◯ Very low	IMPORTANT
ALT				
2	-	See comment	⊕◯◯◯ Very low	NOT IMPORTANT
AST				
2	-	See comment	⊕◯◯◯ Very low	NOT IMPORTANT
Lymphocyte count				
2	-	See comment	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio

[†]without allocation concealment; [‡]included patients <300

[§]I^2=97%

[¶]intervention group (receiving Hydroxychloroquine plus 2 g of Docosahexaenoic acid [DHA] + Eicosapentaenoic acid [EPA]) and an immunonutrient-enriched supplement respectively

[††]included patients <400

[‡‡]one study reported the results as a supplementary figures without specific values

[§§]Control: standard enteral nutrition and placebo (0.9% NaCl) in two groups respectively

[¶¶]one intervention group (receiving Hydroxychloroquine plus 2 g of Docosahexaenoic acid [DHA] + Eicosapentaenoic acid [EPA]) and fish-oil-based lipid emulsion (FOBLE) supplementation in another intervention group

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